CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-246

CORRESPONDENCE

HFD-530

NDA 21-246

Hoffmann-La Roche Inc.
Attention: Barbara S. Taylor, Ph.D.
Program Director
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Taylor

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: TAMIFLU (oseltamivir phosphate) for Oral Suspension 12mg/ml

Review Priority Classification: **Priority (P)**

Date of Application: June 15, 2000

Date of Receipt: June 15, 2000

Our Reference Number: NDA 21-246

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 14, 2000 in accordance with 21 §CFR 314.101 (a). If the application is filed, the user fee goal date will be December 15, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 §CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy. If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 §CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a

waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the Division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy.

Please note that satisfaction of the requirements in 21 §CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 §CFR 314.102(c) of the new drug regulations you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please site the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention Document Control Room
5600 Fishers Lane
Rockville, MD 20857

If you have any question, call Grace N. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely yours

/S/

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 21-246
HFD-530/Division Files
HFD-RPM/Carmouze

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\acklet.doc

ORIGINAL NDA ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Cormourg

Food and Drug Administration
Rockville MD 20857

NOV 7 2000

Monica W. Thint, M.D.
MacGregor Medical Association
4002 Burke Street
Pasadena, Texas 77504

Dear Dr. Thint:

Between August 8 and 10, 2000, Mr. Patrick D. Stone, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #WV15758C) of the investigational drug Tamiflu (oseltamivir phosphate), performed for Hoffman-LaRoche, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Stone discussed with you his observation that for seven subjects you did not perform the required respiratory syncytial virus (RSV) rapid antigen tests prior to enrollment. We note your response in which you stated that in your medical judgement and due to the nature of the RSV test, you elected not to keep the patients longer than necessary to perform the required test. We wish to remind you that in order to rule-out the presence or the absence of RSV, the rapid antigen quick test should have been done.

We appreciate the cooperation shown Investigator Stone during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

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Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:
HFA-224
HFD-530 Review Div.Dir.
HFD-530 MO (Linda Lewis)
HFD-530 PM (Grace Cormouze)
HFD-530 Doc. Rm. NDA #21-246
HFD-45 Reading File
HFD-47 c/r/s GCP File#10193
HFD-47 AEH/KMS
HFR-SW150 DIB (Thornburg)
HFR-SW1540 Bimo (Martinez)
HFR-SW1580 Field Investigator (Stone)

CFN: 16-51566
FEI: 3003099817
Field Classification: NAI
Headquarters Classification:
_____1)NAI
__X _2)VAI-no response required
_____3)VAI-response requested
_____4)OAI

If Headquarters classification is a different classification. explain why:
Deficiencies noted:

_____ inadequate informed consent
_____ inadequate drug accountability
___X _ failure to adhere to protocol
_____ inadequate records
_____ failure to report ADRS ____
_____ other

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r/d:AEH:10/30/00
reviewed:AEH:
f/t:MRB:

Reviewer's Note to Review Division M.O.:

- This site screened a total of 42 subjects; 30 subjects enrolled and 28 completed the study.
- The records for 8 subjects were reviewed in depth; seven out of seven subjects did not receive respiratory syncytial virus (RSV) rapid antigen quick tests to rule-out positive RSV.
- All subjects signed consent prior to study.
- No other discrepancies were observed. Data appear to be acceptable.

FEI: 3003107504
Field Classification: NAI
Headquarters Classification:
___1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
_x__failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-530 Doc.Rm. NDA#21-246
HFD-530 Review Div.Dir.
HFD-530 MO (Linda Lewis)
HFD-530 PM (Grace Carmouze)
HFD-45 Reading File
HFD-47 Chron File; CIB File #10239
HFD-47 AEH/KMS
HFR-CE150 DIB (Eagan)
HFR-CE150 Bimo Monitor (Rashti)
HFR-CE1515 Field Investigator (Tammariello)
r/d:KMS:11/27/00
reviewed:AEH:**(11/27/00)**
f/t:mb:**(11/27/00)**
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Reviewer Note to Rev. Div. M.O.

- This site enrolled 60 subjects with 6 subjects terminating early and 54 subjects completing the study.
- Every subject received informed consent.
- Review of 12 subjects' records found no objectionable conditions.
- No serious adverse events were reported at this site.
- There were no compliance issues found during the inspection that would preclude the use of the data.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Carmenza

Food and Drug Administration
Rockville MD 20857

Sudeep Singh. M.D.
SARC Research Center
7011 N. Howard
Suite 201
Fresno. California 93720

Dear Dr. Singh:

Between August 11 and 15, 2000, Ms. Cynthia L. Evitt representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #WV15758C) of the investigational drug Tamiflu (oseltamivir phosphate), performed for Hoffmann-LaRoche. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated August 21, 2000, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Ms.Levitt presented and discussed with you her inspectional observations. The discussion included the use of an unapproved revised Spanish version of informed consent by the institutional review board and inadequate maintenance of drug dispensing logs. We note your response and your promise to institute appropriate measures to meet FDA regulatory requirements in your ongoing and future studies.

We appreciate the cooperation shown Investigator Levitt during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

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Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II. HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 29-54816
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_X_ _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
__x_inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
__x_inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-530 Doc.Rm. NDA#21-246
HFD-530 Review Div.Dir.
HFD-530 MO (Linda Lewis)
HFD- 530 PM (Grace Carmouze)
HFD-45 Reading File
HFD-47 Chron File
HFD-47 GCP File # 10224
HFD-47 ElHage
HFD-47 Storms
HFR-PA100 DIB (Moss)
HFR-PA150 BIMO Monitor (McGirl)
HFR-PA1500 Field Investigator (Levitt)
r/d:KMS;11/16/00
reviewed:AEH:**(11/16/00)**
f/t:mb:**(11/16/00)**
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Reviewer Note to Rev. Div. M.O.

- This site enrolled 52 subjects with 49 subjects completing the study. 3 subjects were discontinued and no SAEs were reported at this site.
- 12 subjects' files were verified, i.e., sources documents were verified with corresponding CRFs, and those 12 subjects received informed consent.
- Data appear acceptable